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Cognition Enhancers in Age-Related Cognitive Decline

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Summary

A review of recently published studies on the effect of cognition enhancers in non-demented human study participants is presented. The heterogeneity of the therapeutic target, age-associated cognitive decline, can be improved by separately treating groups in whom age-extrinsic factors may underlie cognitive pathology. Standardisation of cognitive assessments is necessary, since many different tests are applied to answer the same question. Modelling cognitive dysfunction, either by pharmacological or nonpharmacological means, in humans is highly recommended since it allows hypotheses to be tested in a clearly oper-

ationalised way. Predictive validity of the currently applied models for the clinical situation remains a problem, however. The scopolamine (hyoscine) model has, to a reasonable extent, predictive validity for the cholinergic agents.

The results of 67 single-dose studies and 30 multiple-dose studies are summarised. All single-dose studies and 14 multiple-dose studies were carried out in young or elderly human volunteers. In 45 of 81 volunteer studies, models of cognitive dysfunction were employed. The scopolamine model was the most used (n = 21); the other studies induced cognitive dysfunction by means of benzodiazepines (8), hypoxia (7), alcohol (5) and sleep-deprivation (4). The remaining 16 multiple-dose studies were clinical trials of a duration varying between 2 weeks and 1 year (average duration was 14 weeks). In these trials, the effects of cognition enhancers were assessed in elderly people in whom impairment of memory, psychomotor performance or cognitive function was determined. These included age-associated memory impairment (AAMI) and age-associated cognitive decline (AACD).

There were many studies in which the cognition enhancing properties of substances in humans were reliably demonstrated. The cognition enhancing properties of substances that are widely used, such as caffeine, nicotine and vitamins, may already be active against AACD. New developments such as serotonin (5-hydroxytryptamine$_3$; 5-HT$_3$) antagonists and *N*-methyl-D-aspartate (NMDA) antagonists have provided marginal and disappointing results in AAMI. There is no cognition enhancer that has reliably and repeatedly been demonstrated to be efficacious for the treatment of AACD. However, this situation may change as the selectivity, specificity and adverse effect profiles of substances that are being developed for the treatment of AD may be expected to be improved in the future.

Cognitive aging, or age-associated cognitive decline (AACD), is a phenomenon that is characterised by the decline of many aspects of cognitive functioning with age.[1-4] There is, however, a considerable variability between individuals as to the rate of cognitive decline. Not only does the physiological aging process influence cognition in the elderly, but also various biological factors such as medical conditions.

There is a borderline between so-called 'normal cognitive aging' and pathological conditions such as dementia, notably Alzheimer's disease (AD), involving disorders of memory and other cognitive functions.[5] Dementia and related pathological conditions, including prodromes of dementia, have a great impact on society because of the financial and organisational consequences for both family and society.[4] Furthermore, the aging of the population results in an increasing prevalence of AACD, and a widespread request for therapeutic agents aimed at least at improving the conditions of cognitive impairment or halting cognitive decline.[6,7]

Unfortunately, although great progress has been made in our understanding of mechanisms of drug action in the brain, and in our understanding of brain changes in elderly people with cognitive deficits or AD patients, a breakthrough in the treatment of these conditions does not seem to be at hand.

Yet, there has been a rapid increase in the interest of clinicians, researchers and the pharmaceutical industry in the development of new classes of drugs designed especially for palliative treatment of AACD and AD-related conditions.[8-10] As a consequence, the number of putative cognition enhancing agents (nootropics) presently under preclinical and clinical investigations is exceedingly high. Hundreds of pharmacological compounds have been developed and tested for their effects on memory in animals, healthy volunteers and AD patients.[11-13]

A problem facing research into the clinical de-

velopment of cognition enhancers is that AACD is not recognised as a disease. No consensus exists as to whether AACD actually should be a therapeutic target for cognition enhancers.[14] The same compounds have been tested in AD patients, governed by the hope that once a drug is registered for that disease, the next step would be to apply it to the treatment of AACD.[15] Furthermore, the questions of whether dementia is the end-point, and AACD or brain aging is the prodrome, are still open.[16]

Although the incidences of both AD and AACD are increasing, the latter accounts for a far larger proportion of the population, and in the last decade of the twentieth century the number of persons over 65 years of age will double. AACD has recently become a diagnostic entity in DSM-IV,[17] and therefore it is likely that the interest in the pharmacological treatment of this condition will revive.

Nootropic properties of drugs were first defined in 1972 by Giurgea[18] as enhancement of learning and memory, facilitation of intercallosal transfer, neuroprotection and a lack of adverse effects. Given this profile, the primary target groups for nootropic treatment consisted of the elderly and people with dementia. Since then, many substances have been developed with the same aim, but they do not fulfil the above definition of nootropic drugs. These are therefore called cognition enhancers, which are defined primarily in terms of their effect. Cognition enhancement can also be achieved by psychostimulants and antidepressant drugs, but we do not refer to these as cognition enhancers as this is not their most characteristic feature.

Nowadays, the term nootropic drugs usually refers only to the piracetam-like compounds which contain the 2-oxopyrrolidineacetic acid derivative (racetam) substructure.[19]

In the past 5 years, numerous controlled experiments and clinical trials in demented, but also in non-demented, physically healthy humans, young and old, with or without AACD, have been conducted. Excellent updates, summarising most of the modern research in cognition enhancers in animals[12,20] and in patients suffering from AD,[13,21] have recently been published.

Sarter and colleagues[12,20] explained difficulties that have emerged in the search for drugs to enhance cognitive performance in patients with dementia and in aged individuals. A systematic and rigorous evaluation of validity (predictive, face and construct) for the animal models most frequently used in preclinical research, was deemed a necessary prerequisite for further research. Giacobini and Becker[21] categorised putative cognition enhancers for the treatment of AD, into the following groups:

- drugs that survived (cholinesterase inhibitors);
- drugs that revived (muscarinic agonists);
- drugs that never made it (nootropics, cholinergic function enhancers, acetylcholine releasers and modulators, neuropeptides, and hormone precursors and growth factors);
- unfulfilled promises (calcium uptake blockers or antagonists, glutamate agonists/antagonists, antioxidant compounds and anti–β-amyloid drugs); and
- winner drugs (second- and third-generation cholinesterase inhibitors with higher selectivity and specificity).

We have attempted to review the results from controlled experiments and clinical trials with cognitive enhancers in humans without dementia that have been published since 1990. Two general questions governed the review process. The first question was the cognition enhancers' proof of existence: do they work? – i.e. do cognition enhancers indeed enhance cognition? The second question addressed the search for underlying (brain) mechanisms: if cognition enhancers work, how do they work? In this paper, we can translate the latter question into: which particular compounds work more than others, as specified in terms of the mechanism that they manipulate?

In section 1, the patient groups, from healthy young volunteers to elderly patients with memory complaints or cognitive disorders, are described. A distinction is made between experiments performed under normal conditions and experiments

performed under conditions intended to model AACD. In section 2, the dependent measures used in most studies, cognitive and psychomotor tests, clinical and psychophysiological [electroencephalogram (EEG)] assessments, are briefly described. In section 3, a review of studies whose primary aim was to investigate the claim of substance-induced cognition enhancement in individuals without dementia is presented.

This was accomplished by performing literature searches in the various relevant journals themselves as well as their abstracts published on *MedLine*, *PsycLit* and *Excerpta Medica/Embase* from 1990 until March 1995. As far as possible, abstract books of congresses covering the subject matter were searched for relevant contributions, and our own nonsystematic exposure to knowledge about experiments and trials with cognition enhancers was utilised. In the last 2 sections, discussion and concluding remarks respectively, the results are put into perspective.

1. Patients and Experimental Models

1.1 Patient Populations

In our previous paper on cognitive impairment in elderly people,[4] several concepts, such as benign and malignant senescent forgetfulness,[22] age-associated memory impairment (AAMI),[23] late-life forgetfulness and age-consistent memory impairment,[24] were described in an effort to identify the target population of elderly people with cognitive aging. Since the proposal of the criteria for AAMI,[23] this has been the most used description, particularly in drug trials. However, according to some of the many criticisms,[8,24-28] the AAMI criteria classify some 67% of the population over 50 years of age as having this disorder. Recently, stricter criteria for the condition AACD have been published.[17]

Other populations which have been studied may be described by:

- elderly patients with impaired cognitive function;[29]
- elderly patients with pronounced memory problems of unknown origin;[30]
- elderly deficient drivers;[31,32]
- memory-disturbed patients;[33]
- elderly patients with mild to moderate memory impairment according to NINCDS-ADRDA criteria.[34-36]

These are variations on the same theme, albeit that the first 2 seem to include more severe cases and hence truly constitute the borderline between normal and pathological aging.

Furthermore, some studies have been published on the effects of cognition enhancers in other neuropsychological populations, such as patients with epilepsy, organic brain syndrome after prolonged exposure to organic solvents or after alcoholism, in which alleviation of cognitive dysfunction was the prime target of drug therapy.

Many studies have been conducted on the effects of cognition enhancers in volunteers; these can be subdivided into those conducted in the young and the elderly. The rationale behind studying the effects of cognition enhancers in healthy elderly volunteers does not differ very much from that of studying cognition enhancers in patients with AAMI. It is often assumed that normal elderly volunteers are also affected by, but not necessarily suffering from, cognitive aging. In addition, studies of cognition enhancers in elderly volunteers yield the pharmacokinetic and tolerability data appropriate for that age group.

In most of the studies into the effects of cognition enhancers in healthy young volunteers, specific experimental manipulations or paradigms are applied to induce aspects of cognitive dysfunction.

1.2 Experimental Models

Understanding AACD and treating it pharmacologically calls for the wish to be able to model its presumed mechanism and hence predict the therapeutic response of putative cognition enhancers. Several human models have been the subject of debate, particularly the scopolamine (hyoscine), benzodiazepine and hypoxia models of cognitive dysfunction.[37-39]

The major problem in predicting clinical efficacy from human experimental results and phase I data is the lack of resemblance between the models used and the clinical condition. This problem is complicated by the diversity of the potential mechanisms of action of new compounds. A further question is whether phase I studies should be used as predictors of clinical efficacy at all. It has nonetheless been suggested that some human models (e.g. scopolamine-induced amnesia, hypoxia-induced performance deficits) are indeed potential predictors of clinical response.[38] These models have, in the past 5 years, frequently been used in the process of screening the effects of cognition enhancers in humans.

1.2.1 The Scopolamine Model

Deterioration of cholinergic system functioning has been postulated to contribute to memory impairment in normal aging and AD.[40,41] The anticholinergic drug scopolamine, which acts by blocking muscarinic acetylcholine receptors, has been used to study the role of acetylcholine in attention and memory and to model aspects of the memory and other cognitive changes that occur with aging.[42-46] Scopolamine-induced cognitive dysfunction, which consists largely of memory dysfunction, has been shown to be reversible when drugs stimulating the cholinergic system are administered concomitantly.[47-50] However, this effect is not always found with CNS stimulants,[51-54] which is another indication that anticholinergic effects are specifically related to impaired memory function.

1.2.2 The Benzodiazepine Model

Anterograde amnesia is a well-known adverse effect of the benzodiazepines.[55] These transient drug-induced effects have been related to clinical attentional and memory deficits,[56] and to dementia.[57] Amnesia caused by benzodiazepines may provide a useful model for some organic amnesias and thereby allow strategies to be developed for treating these amnesias.[58] Furthermore, the rationale has been proposed that β-carbolines with antagonist or partial inverse agonist properties at the γ-aminobutyric acid (GABA) benzodiazepine receptor complex may offer a treatment for senile dementia.[57]

1.2.3 The Hypoxia Model

The CNS is particularly sensitive to hypoxia with resultant demonstrable effects on cognitive function.[59] Most models of hypoxia and ischaemia are used for evaluating the metabolic consequences of cerebral insult.[60] They have also been used for inducing cognitive disturbance.[61] The pathological cascade after severe hypoxia or ischaemia includes decreased ATP and influx of Ca^{++} and Na^{+} with decrease in intracellular K^{+}, leading to depolarisation, release of glutamate, noradrenaline and acetylcholine, changes in neuronal plasticity, cell death and cognitive impairment.[62] Possible pharmacological mechanisms for protecting brain function include blockade of Ca^{++} influx, inhibition of cell swelling, regulation of membrane potential, inhibition of neurotransmitter release and inhibition of excitatory amino acid receptors.[62]

1.2.4 Acute Ethanol Intoxication

The behavioural toxicity of alcohol in humans is characterised by impaired performance on a great number of cognitive tasks.[63] Alcohol-induced memory deficits have been claimed to mimic age-related memory deficits because of their functional similarity as to the state of depleted processing resources.[64] The central effects of alcohol have also been said to be mediated through the GABA system and hence to resemble those of benzodiazepines.[65] Furthermore, alcohol may induce histotoxic (as opposed to hypoxic) hypoxia since it reduces the oxygen uptake of tissue cells.[66]

1.2.5 Sleep Deprivation

Functional similarities have been postulated between AACD and sleep deprivation, and also that memory deficits in these conditions are more likely to occur in tasks which require a lot of thought rather than automatic processes.[64] Lowering arousal, by means of sleep deprivation, is a frequently used task manipulation in order to induce depletion of cognitive processing resources.[67]

The decline in cognitive performance during sleep deprivation has been shown to be mediated by brain catecholamines.[68]

2. Dependent Variables in Experiments and Clinical Trials

2.1 Cognition

Observable behaviour as a function of physical stimuli, interconnected by an unobservable 'black box', was roughly the psychology of the behaviourists. Nowadays, psychology is the science of cognition, the black box between stimulus and response. Cognition is the label for all processes that mediate nonreflexive behaviour in living organisms.

The central theme of cognitive psychology is that of the organisms' internal representation of the outside world.[69] For example, novice and experienced clinicians differ in the way they perceive their patients and subsequently form their diagnoses. The explanation is not that their perception is different, but their internal representation of the problem, to which their perception is compared, differs.

The cognitive explanation is that perception, judgement, decision and overt response are governed by expectations, based on prior knowledge and experience.[70] Thus, an internal representation cannot exist without memory. Perceived images are stored in working or short term memory and compared with knowledge retrieved from long term memory. Although memory is known to reside in the brain, it is certainly not one observable organ, but its vital functions, such as storage, search, consolidation and retrieval, can be assessed using neuropsychological tests, EEG measures, clinical ratings or elaborate computerised methods.

The vulnerability of memory is illustrated by the gradual, but in the end complete, disruption of this cognitive system in patients with dementia. It is therefore logical that most trials investigating the efficacy of cognition enhancers primarily aim to assess improvements of memory functions.

2.2 Cognitive Performance

There is no uniformity in the test procedures or experimental tasks to evaluate the efficacy of cognition enhancers.[71] The way in which memory processes or cognitive functioning has been operationalised differs amongst the studies.

The most frequently used procedure is word list learning. The relevance of a word learning task for cognitive pharmacology is that this task provides the possibility to examine the effectiveness of retrieval strategies. As such, the multi-trial free recall procedure is a powerful paradigm to examine verbal memory processes.[72]

Unfortunately, as in the presentation of word list learning procedures, standardisation has been lacking. Some studies only refer to the word list learning procedure without specification of how many words were used or how often the list of words was presented. Specification of procedures such as delayed recall and delayed recognition was often lacking. Some studies did report the number of words in the list, but no information was given about whether parallel lists were used. Some studies explicitly reported the use of the Rey Auditory-Verbal Learning Test,[73] a standardised procedure, while others only mentioned the use of a 15-word learning test, without further specification.

The evaluation of drug effects over studies is thus hindered by the lack of uniformity in the procedures used. The number of words per list, the rate of presentation, the retention interval, the number of monosyllables versus bisyllables, the frequency of the words in the native language and other variables also vary across studies.

A well-defined procedure which differs from the Rey procedure is the Buschke's Selective Reminding Method.[74] In this procedure, parallel lists are used, consisting of 15 related nouns. The patient has to recall the list within 1 minute. Nouns that are left out by the patient are read again by the experimenter. This is done repeatedly for 10 trials (but less in many studies). The procedure provides information about short term memory, long term memory and the retrieval strategy.

Another frequently used test of visual memory is the Benton Visual Retention Test. The test, however, has been subject to criticism, because it is not very sensitive. Moreover, it is disputed that the test measures immediate visual memory and the notion is supported that it is a test of visuomotor performance.[71]

The second most important paradigm in memory assessment is perhaps the well known Sternberg paradigm, in which the speed of retrieval from short term memory is measured.[75] This is accomplished by instructing the patient to compare new stimuli with target stimuli held in short term memory (memory set). By repeating the tests while increasing the memory set, measures reflecting the speed of scanning 1 item in short term memory are obtained separately from the offset speed component of the task, which is not memory-related. This task has been shown to be very sensitive to aging.[76] Noncomputerised versions of this principle are also available. The task is interesting because it allows separate estimates, obtained in 1 test, of speed of memory- and non–memory-related information processing.[77]

The operation of the different aspects of memory is poor in most studies investigating cognition enhancers. Testing has been done with numerous different procedures. Standardisation and a description of the procedures are often lacking. Testing procedures from experimental psychology should be used when aspects of memory processes would be better suited to assess the underlying biological mechanisms. Standardised procedures of memory testing with well-evaluated parallel test versions can be regarded as an essential prerequisite for an experimental study into the efficacy of a cognition-enhancing drug.

2.3 EEG Measures

A distinction must be made between EEG assessed at rest, the so-called background EEG, and task-related measures such as those obtained using the event-related potentials (ERP) paradigm, of which the P300 is the most used. The latter seem to be more important, since changes in EEG activity when patients are at rest point primarily to changes in vigilance and not necessarily cognition. Nevertheless, background EEG-measures after the administration of cognition enhancers are used quite often, especially applied in models of cognitive dysfunction. The background EEG has been used in a number of trials primarily with the aim of assessing the brain bioavailability of cognition enhancers, and also offers the possibility of evaluating the distribution of changed activity over the different regions of the cortex.[78]

Brain imaging techniques which yield quantitative measures of regional brain function (or metabolism), such as positron emission tomography (PET) and single photon emission computerised tomography (SPECT), may be superior at determining the location in space (i.e. where in the brain) of drug-induced changes. Task-related EEG measures, ERPs, are superior in terms of location in time (i.e. speed of cognitive processing) of drug-induced changes. The P300 is perhaps the best measure of drug-induced changes in cognitive processes in the brain, as compared with measures of cognitive test performance which are the end-products of those processes.

2.4 Clinical Ratings

Some investigators have evaluated efficacy with the help of clinical rating and mood scales, such as the Mini–Mental State Examination or the Sandoz Clinical Assessment–Geriatric. The true end-products of all cognitive and noncognitive processes are reflected in clinical rating scales. The most typical of these is the Clinical Global Impression, which reflects the judgement of the clinician about a patient's mental status, expressed on a scale of 1 to 7. Although the title of the scale suggests that it is always the clinician who performs the ratings, subjective ratings by the patient are also included, and there is a growing number of trials in which ratings of the partners or carers of the patients are used as primary measures of outcome.

An important development in clinical trials of AD is the 'Clinician's Interview-Based Impression of Change' (CIBIC). It is doubtful whether this

measure would be sensitive in AACD. Applied in placebo-controlled double-blind drug trials, however, these ratings can, in general, be sensitive but highly nonspecific indicators of drug effects.[15]

Clinical rating scales are generally seen as the counterbalance against the often heard criticism that cognitive performance tests as well as EEG measures yield, at most, microscopic changes that can never been seen through the naked eye. This phenomenon is most obviously present in clinical research in AD patients, where, even though the claim of AD being a memory or cognitive disease is still always made, clinical assessments are far more important than any of the cognitive or process measures.

3. An Overview of Cognition Enhancers in Single- and Multiple-Dose Studies

The results of experiments and clinical trials with cognition enhancers in humans without dementia can be categorised along several dimensions, such as population studied, type of drug, dosage used and duration of the study. We chose to make a distinction between 67 single-dose studies and 30 multiple-dose studies, which are listed in tables I and II, respectively. All studies are at least single-blind and controlled with placebo or an active drug.

Nearly all single-dose studies were carried out in healthy volunteers. In 45 of the volunteer studies, models of cognitive dysfunction were employed. The scopolamine model was the most used (n = 21), while the other studies induced cognitive dysfunction by means of benzodiazepines (8), hypoxia (7), alcohol (5) and sleep deprivation (4). Most multiple-dose studies were carried out in elderly people, volunteers (n = 10) and patients (20), with cognitive impairment.

The main modes of action of the classes of cognition enhancers studied are described below, as well as the major results obtained from the multiple-dose studies.

3.1 Nootropic Agents

Even recent reviews of piracetam and related compounds state explicitly that, in spite of a tremendous amount of research in the latter 30 years, no commonly accepted mechanism of action has been established.[19,151] Some benefit of piracetam-like nootropics in clinical studies of patients with mild to moderate degrees of dementia has been demonstrated, although the clinical response is estimated to lie in the 10 to 30% range.[152] The possible modes of action of nootropic drugs can be grouped in 4 categories:[152]

- Effects on energy metabolism, such as increased adenylate kinase activity and increased glucose utilisation in hypoxic and anticholinergic conditions.
- Effects on cholinergic mechanisms, such as increased high-affinity choline uptake and increased density of cortical muscarinic receptors.
- Effects on excitatory amino acid receptor-mediated functions, such as increased hippocampal glutamate release and potentiation of the AMPA-induced calcium influx by means of AMPA receptor stimulation.
- Steroid sensitivity, which was shown by the absence of nootropic effects in adrenalectomised animals and by the blockade of nootropic effects by pretreatment with steroid hormones.

After 30 years, there are still new results published about the effects of piracetam and its successors. A clinical trial in individuals without dementia with mild to moderate memory impairment yielded positive effects for piracetam 3 and 6 g/day on tests of attention and memory, and also clinical improvement.[35] An interesting combination of treatment with piracetam 2.4 and 4.8 g/day with memory training therapy showed that combined therapy was most effective with the 4.8 g/day dose in patients whose baseline performance on memory tests was lowest.[131] Despite the intriguing combination of drug treatment with a memory training programme, it must be noted here that a *post hoc* split-half analysis in order to evaluate treatment effects is a dubious practice which invalidates the analysis.

The 2 studies of piracetam 4.8 g/day on the ability of deficient elderly drivers to perform tests of car driving in real traffic[31,32] were, in this sense, more adequate. In both studies, elderly people were selected on the basis of objectively assessed deficits in psychomotor performance. In the first study, selection was based on psychomotor test performance below the median of the age reference group. This study showed that piracetam treatment reduced the number of errors made in real traffic, compared with placebo treatment.[31]

In the second study, elderly patients were selected on the basis of 'deficient' performance in 1 established driving test in real traffic and scoring below the median on another. This study showed no beneficial effects of piracetam on car driving performance. However, enhanced postural stability after piracetam showed that the drug was active.[32]

If drugs improve postural stability, there is evidence that the central availability of cognitive processing resources is supplemented,[153,154] and hence cognitive enhancement could be the result. Such a hypothesis seems prominent in the case of the piracetam-like drugs and could very simply be tested by having the patients' cognitive performance tested in a standing position while simultaneously measuring their postural stability. However, this has never been done to our current knowledge. There is some evidence that the more recently developed drugs in this category, such as pramiracetam, are more potent and perhaps more efficacious.

In 1991, a review of the therapeutic use of piracetam in senile cognitive disorders concluded that the clinical usefulness of the drug was the subject of much debate because it continued to give mixed results.[151] In the light of what is presented here, this does not appear to have changed.

Pramiracetam 600mg administered twice daily during a 12-week period to elderly patients with memory impairment led to significant improvements in memory performance relative to placebo.[34] Pramiracetam 600mg administered twice daily during a period of 10 days, when compared with placebo, was able to partially reduce the amnesic effects induced by scopolamine both in young (18 to 42 years) and elderly (55 to 65 years) patients.[132]

3.2 Ergot Alkaloids

Ergot alkaloids exert direct action at α-adrenergic, dopamine and serotonin receptors. They appear to have a normalising effect on central monoaminergic neurotransmitter systems, compensating for both hyperactivity and deficits of the adrenergic, serotonergic and dopaminergic systems. Ergot alkaloids have marked pre- and postsynaptic α-adrenoceptor antagonist activity, with higher affinity for α_2- than α_1-receptors, and mixed agonist/antagonist effects at dopamine D_1 and D_2 receptors and at serotonergic (5-HT_1 and 5-HT_2) receptors.[155]

Ergoloid mesylates (codergocrine mesylate) is a combination of the mesylated forms of dihydroergocornine, dihydroergocristine, dihydro-α-ergocryptine and dihydro-β-ergocryptine. In a double-blind placebo-controlled trial using the hypoxia-model, a single dose of ergoloid mesylates 5mg administered to 12 healthy young volunteers significantly attenuated hypoxia-induced brain dysfunction and psychometric performance.[84] In a similar subsequent trial, further augmentation of the severity of hypoxia resulted in a loss of brain protection, even when ergoloid mesylates was given daily over 2 weeks.[84]

A review of the results from controlled studies of elderly patients with AACD established that, in some studies, ergoloid mesylates had statistically significant positive effects on symptoms of cognitive dysfunction. Nevertheless, the specific place of ergoloid mesylates in the treatment of age-related cognitive decline remains undetermined, despite many years of clinical use.[155]

The central hypothesis underlying the cognition enhancing properties of the ergot alkaloids is that of improved brain perfusion. Notwithstanding the fact that there is at least some evidence of a weak effect of the drug, there is no clinical study that clearly confirms the cognition enhancing effects

Table I. Single-dose studies of cognition enhancers conducted in volunteers

Family and class	Compound	Dose range and route	Condition/ experimental model	n	Study design	Age (y)	Assessments	Outcome	Reference
Nootropic agents									
Pyrrolidinones	Aniracetam	2-200mg IV	Scopolamine (hyoscine)	26	co	19-34	Cogn	0	80
	Aniracetam	1500mg PO	Scopolamine	26	co	19-34	Cogn	+	80
	BMS 181168	100-400mg PO	Hypoxia	16	co	23-35	EEG	+	83
	Oxiracetam	800-2400mg PO	Scopolamine	12	co	21-30	Cogn	+	82
	Piracetam	2.9-9.6g PO	Healthy	6	co	30-47	Cogn + EEG	+	79
	Piracetam	2.4g PO	Scopolamine	26	co	19-34	Cogn	0	80
	Piracetam	12g IV	Hypoxia	18	co	Young[a]	Cogn + EEG	+	81
	Piracetam	12g in syrup	Hypoxia	18	co	Young[a]	Cogn + EEG	+	81
Ergot alkaloids									
Vasoactive agents	Ergoloid mesylates (codergocrine mesylate)	5mg PO	Hypoxia	15	co	Young[a]	Cogn + EEG	+	84
	Ergoloid mesylates	5mg PO	Hypoxia	12	co	Old[a]	Cogn + EEG	+	85
	Nicergoline	30 or 60mg PO	Hypoxia	12	co	Old[a]	Cogn + EEG	+	85
	Voxergolide (RU 41656)	10mg PO	Scopolamine	12	co	19-30	Cogn	0	86
	Voxergolide	10mg PO	Triazolam	12	co	19-36	Cogn	0	87
Neuropeptides									
ACTH analogues	Ebiratide	60, 300 or 600g IV	Healthy	16	co	Old[a]	Cogn	0	90
	Ebiratide	60, 300 or 600g IV	AAMI	24	co	Old[a]	Cogn	+	90
	Ebiratide	60,300 or 600g IV	AAMI	20	co	Old[a]	Cogn	+	91
	ORG 5667 (desglycinamide arginine vasopressin)	2mg IN	Healthy	12	pg	Young[a]	Cogn	+	88
	ORG 5667	2mg IN	Healthy	43	pg	21.6	Cogn	+	89
TRH analogues	Protirelin	0.5 mg/kg IV	Scopolamine	12	co	26.9	Cogn	+	92
	Protirelin	0.5 mg/kg IV	Lorazepam	?	?	?	Clin	+	93
Cholinergic agents									
Anticholinesterases	Eptastigmine	20 or 32mg PO	Scopolamine	24	co	21-45	Cogn	0	97
	Physostigmine	2mg PO	Scopolamine	24	co	Young[a]	Cogn	+	94
	Physostigmine	1.5mg IV	Healthy	12	co	22-38	Cogn + EEG	+	95
	Velnacrine	100 or 150mg PO	Scopolamine	31	co	Young[a]	Cogn	+	96
Cholinomimetics	Thiopilocarpine (SDZ ENS 163)	50mg PO	Healthy	18	co	Young[a]	Cogn	0	98
Nicotinic agonists	Nicotine	0.75 or 1.5mg PO	Healthy	19	co	18-30	Cogn	+	99
	Nicotine	2 or 4mg gum	(Non)smokers	11	co	?	Cogn	0	100

	Nicotine	2mg gum	Acute alcohol intoxication	10	co	?	Cogn	+	101
	Nicotine	1.5mg PO	Scopolamine	19	co	18-30	Cogn	0	99
	Nicotine	0.5-1mg IV	Sleep deprivation	35	pg	21-41	Cogn	±	102
	Nicotine	2 cigarettes	Smokers	48	co	?	Cogn	+	103
	Nicotine	0.8mg SC	Nonsmokers	12	co	21-33	Cogn + EEG	±	104
	Nicotine	2mg gum	Scopolamine	16	co	25-33	Cogn	+	105
Monoaminergic agents									
α_2-Antagonists	Idazoxan	15mg IV	Healthy	8	co	24-30	Cogn	+	107
MAO-A inhibitors	Moclobemide	400mg PO	Scopolamine	28	co	?	Cogn	+	109
MAO-B inhibitors	Selegiline (deprenyl)	20 or 30mg PO	Sleep deprivation	31	pg	21-41	Cogn	±	102
Serotonin 5-HT_3 antagonists	GR 66755	10 or 250g PO	Scopolamine	12	co	18-37	Cogn	+	108
Sympathomimetics	Dexamphetamine	10mg PO	Retention	60	co	19-25	Cogn	+	106
	Dexamphetamine	5, 10 or 20mg PO	Sleep deprivation	36	pg	21-41	Cogn	+	102
GABA-ergic agents									
Benzodiazepine antagonists	Flumazenil	0.5mg IV	Midazolam	16	co	21-43	Cogn	+	110
	Flumazenil	5mg IV	Alcohol	8	co	23-32	Cogn	0	64
	Flumazenil	1 or 3mg IV	Midazolam	72	co	18-40	Cogn	+	111
	Flumazenil	0.035 mg/kg IV	Diazepam	8	co	24-31	Cogn	±	112
β-Carbolines	ZK 93426	0.04 mg/kg IV	Scopolamine	40	pg	18-42	Cogn	0	113
Aminoacidergic agents									
NMDA antagonists (glycine agonists)	Cycloserine	5, 15 or 50mg PO	Scopolamine	23	co	63-75	Cogn	+	114
	Cycloserine	5, 15mg PO	Healthy	24	co	63-75	Cogn	0	115
	Cycloserine	5, 15 or 50mg PO	Scopolamine	24	co	18-31	Cogn	+	116
	Milacemide	400mg PO	Healthy	33	pg	Young[a]	Cogn	–	117
Methylxanthines									
Adenosine$_{A1}$ antagonists	Caffeine	250mg PO	Healthy	20	co	60-77	Cogn	+	118
	Caffeine	250mg PO	Acute alcohol intoxication	10	co	?	Cogn	+	101
	Caffeine	300mg PO	Triazolam	?	co	?	Cogn	+	119
	Caffeine	300mg PO	Zopiclone	?	co	?	Cogn	±	119
	Caffeine	3.3 mg/kg PO	Alcohol	9	co	?	Cogn	+	120
	Caffeine	250 or 500mg PO	Triazolam	9	co	18-29	Cogn	+	121
	Caffeine	250mg PO	Healthy	15	co	18-25	Cogn + EEG	±	122

continued on next page

Table I. Contd

Family and class	Compound	Dose range and route	Condition/ experimental model	n	Study design	Age (y)	Assessments	Outcome	Reference
	Caffeine	250mg PO	Sleep deprivation	15	co	18-25	Cogn + EEG	+	123
	Caffeine	250mg PO	Scopolamine	16	co	25-33	Cogn	+	105
	Enprofylline	1.5 mg/kg IV	Healthy	12	co	18-40	Cogn	0	124
	Theophylline	250mg PO	Healthy	20	co	60-77	Cogn	+	118
	Theophylline	5 mg/kg IV	Healthy	12	co	18-40	Cogn	+	124
Vitamins									
	Thiamine	5g PO	Scopolamine	13	co	23-35	Cogn + EEG	+	125
Miscellaneous									
ACE inhibitors	Enalapril	2.5 or 10mg PO	Scopolamine	35	co	18-42	Cogn	0	130
Calcium antagonists	Nifedipine	20mg PO	Healthy	10	co	21-25	Cogn	0	129
Metabolic enhancers	Glucose	50g PO	Healthy	153	pg	21.7	Cogn	+	126
Phospholipids	Phosphatidylserine	25, 50 or 75mg IV	Healthy	8	co	21-28	Cogn + EEG	±	127
	Phosphatidylserine	10 or 25g PO	Healthy	83	co	20.3	Cogn	+	128

a Specific age not reported.

Abbreviations and symbols: AAMI = age-associated memory impairment; ACTH = adrenocorticotrophic hormone; co = crossover; cogn = cognition; EEG = electroencephalogram; IN = intranasal; IV = intravenous; MAO = monoamine oxidase; pg = parallel groups; PO = oral; SC = subcutaneous; TRH = thyrotropin-releasing hormone; ? = unknown; 0 = no effect; + = positive effect; ± = partial effect; – = negative effect.

simultaneously with the assessment of improved brain perfusion.

Several examples of protection by an ergot alkaloid against disturbed brain perfusion using the hypoxia model were obtained from single-dose studies. The study that addressed this problem in perhaps the best possible way, by applying the hypoxia model at the end of subchronic treatment with ergoloid mesylates, did not show the desired effect.[84]

3.3 Neuropeptides

Several neuropeptides, namely adrenocorticotrophic hormone (ACTH) and thyrotropin-releasing hormone (TRH) analogues, have been shown to exert significant effects on motivational, learning and memory processes.[11] The effects of corticotrophin (exogenous ACTH) appear to be independent of its endocrinological action on the adrenal cortex.

Neuropeptides related to the pituitary hormone vasopressin have also received profound interest.[156] A series of 5 consecutive clinical trials was published in which the neuropeptide ORG 5667 (desglycinamide arginine vasopressin; DGAVP) was administered to 64 patients with cognitive and memory complaints. The patients selected for the study were carefully screened with the aid of neuropsychological assessment procedures. The trials were conducted according to a structured design in which the variables 'dose', 'route of administration', 'treatment schedule', 'diagnostic group' and 'severity of deficit' were altered from trial to trial in order to find optimal conditions for the possible expression of a peptide effect.

The results indicated a statistically significant effect of ORG 5667 on word list learning in patients with mild brain trauma, suggesting that learning performance and memory retrieval were improved after peptide treatment in these patients. Some effects of ORG 5667, e.g. increased speed of memory search, were observed in patients with age-associated memory deficits.[33] ERPs were recorded in 22 elderly and 28 young patients who received 10IU of argipressin (arginine vasopressin)

intranasally 22, 12 and 1 hour(s) prior to experimental sessions. The results indicated that argipressin improved ERP signs of stimulus processing associated with attentional mechanisms. However, the ERP signs of AACD remained unimproved after argipressin.[133]

3.4 Cholinergic Agents

The cholinergic hypothesis of geriatric memory dysfunction entails that cognitive decline can be counteracted by enhancement of central cholinergic function.[40] This hypothesis has stimulated interest in cholinergic function of the brain in relation to human cognition and AACD. It is unclear whether normal aging results in a loss of cholinergic innervation to cerebral cortex and hippocampus, as in AD, but the prevailing evidence suggests that certain aspects of brain cholinergic function are diminished with advancing age.[157]

Cholinergic receptors in the brain are of the muscarinic and nicotinic type and there are muscarinic and nicotinic agonists that stimulate these 2 subtypes of acetylcholine neurotransmission. Selective compounds that are specifically aimed at muscarine m_1 receptor subtypes have been developed and these represent a new avenue in the treatment of AD. Studies in humans have been reported to show the selectivity and specificity of these agents but, unfortunately, reports on their cognitive effects in humans are lacking.[158] The main development in nicotinic agonists is reflected by the interest in the influence of nicotine on cognition.[159,160]

An additional therapeutic avenue is to use precursors of acetylcholine to increase the synthesis of acetylcholine in the brain. Cholinesterase inhibitors increase acetylcholine neurotransmission by means of inhibiting the activity of the enzymes that normally degrade acetylcholine. Cholinesterase inhibitors are currently in the focus of interest since tacrine was approved for use in the treatment of dementia of the Alzheimer type, the first drug to be registered for this purpose.[161] This has stimulated research with cholinergic agents in general and cholinesterase inhibitors in particular; second and third generations of these compounds are currently being studied and developed.[162] Because of their adverse effect profile, these agents are perhaps less interesting in relation to the treatment of AACD, but the results obtained in phase I studies with healthy volunteers are interesting from a theoretical and methodological point of view.

The influence of 4 weeks' treatment with the cholinesterase inhibitor huperzine A 200 to 400 μg/day on memory complaints when administered to 101 patients with benign senescent forgetfulness was found to be superior to that of piracetam 2.4 to 3.2 g/day.[134] The effects of repeated doses of linopirdine 20mg (a phenylindolinone derivative enhancing the release of acetylcholine in cholinergic nerve terminals) administered twice a day over a 10-day period were investigated in 30 elderly men. EEG showed significant central effects of linopirdine, indicative of an improvement in vigilance.[135]

The relative success of cholinesterase inhibitors as a palliative treatment in AD is not so apparent in AACD. A high incidence of adverse events, particularly hepatotoxicity, combined with relatively few possibilities for cognitive improvement, has led to a negative cost-benefit ratio of these agents in AACD. This situation could change if second- and third-generation cholinesterase inhibitors developed for the treatment of AD lack the adverse event profile that is characteristic of tacrine.[161] This seems to be the case for huperzine A,[134] but more data demonstrating the efficacy of the drug need to be gathered.

Experiments using the scopolamine model of cognitive dysfunction have shown that cholinesterase inhibitors can completely reverse cholinergic deficits in humans, whereas the influence of most other substances tested using this model are reported in terms of a significant attenuation. If a substance shows no effect in the model, its development, at least in the doses studied, should be halted. The predictive validity of the scopolamine model is perhaps the highest in cholinesterase inhibitors. Furthermore, despite a frantic search, no scopolamine trial in humans could be found dem-

Table II. Multiple-dose studies and clinical trials of cognition enhancers

Family and class	Compound	Dose range and route	Duration	Study participants	Condition/ experimental model	n	Study design	Age (y)	Assessments	Outcome	Reference
Nootropic agents											
Pyrrolidinones	Piracetam	2.4-4.8 g/day PO	12wk	Patients	AAMI	135	pg	>55	Cogn	+	131
	Piracetam	3 or 6 g/day PO	22wk	Patients	AACD	84	co	65-80	Clin + cogn	+	35
	Piracetam	4.8 g/day PO	4wk	Patients	AACD	39	co	60-79	Driving	0	32
	Piracetam	4.8 g/day PO	6wk	Volunteers	AACD	96	pg	48-76	Driving	+	31
	Pramiracetam	600mg bid PO	12wk	Patients	AAMI	60	pg	60-84	Clin + cogn	+	34
	Pramiracetam	600mg bid PO	10 days	Volunteers	Scopolamine (hyoscine)	24	pg	18-65	Cogn	+	132
Ergot alkaloids											
Vasoactive agents	Ergoloid mesylates (codergocrine mesylate)	5 mg/day PO	2wk	Volunteers	Hypoxia	12	co	Young[a]	EEG + cogn	0	84
Neuropeptides											
Vasopressin analogue	Argipressin (arginine vasopressin)	60IU bid IN	2 days	Volunteers	Healthy	50	pg	Young/old[a]	EEG	±	133
	ORG 5667 (desglycinamide arginine vasopressin)	0.1-1 mg/day IN	4wk	Patients	Memory disturbed	64	co	18-70	Cogn	±	33
Cholinergic agents											
Acetylcholine releasers	Linopirdine	20mg bid PO	10 days	Volunteers	Healthy	30	pg	60-80	EEG	+	135
Cholinesterase inhibitors	Huperzine A	200-400 g/day PO	4wk	Patients	AAMI	101	pg	50-89	Clin	+	134
Monoaminergic agents											
α_2-Agonists	Almitrine/raubasine	?	6mo	Patients	AACD	204	pg	70-85	Clin + cogn	0	137
	Guanfacine	0.5 mg/day PO	4wk	Patients	AAMI	40	pg	50-79	Clin + cogn	0	136
	Guanfacine	0.1-0.4 mg/day PO	4wk	Patients	AAMI	160	pg	>50	Clin + cogn	0	136
Noradrenaline enhancers	S 120242	10-500mg bid PO	7 days	Volunteers	Healthy	45	pg	>60	Cogn	+	138
Serotonin 5-HT_3 antagonists	Ondansetron	0.01, 0.25 or 1mg bid PO	12wk	Patients	AAMI	198	pg	50-80	Clin + cogn	+	139
Aminoacidergic agents											
NMDA antagonists (glycine agonists)	Cycloserine	1, 5 or 15mg bid PO	12wk	Patients	AAMI	330	pg	>50	Clin + cogn	0	140
	Milacemide	1200 mg/day PO	2 days	Volunteers	Healthy	32	pg	19-34	Cogn	+	141
	Milacemide	1200 mg/day PO	2 days	Volunteers	Healthy	32	pg	60-78	Cogn	+	141

Vitamins											
	Multivitamins		1y	Volunteers	Healthy	127	pg	17-27	Cogn	+	142
	Pyridoxine	20 mg/day PO	3mo	Volunteers	Healthy	76	pg	70-79	Cogn	+	143
	Pyritinol	600 or 1200 mg/day PO	3 days	Volunteers	Healthy	12	co	19-26	Cogn	+	144
Herbal compounds											
Flavanoids, terpenoids	Ginkgo biloba extract	40, 80 or 160mg tid PO	3 days	Volunteers	Healthy	24	co	24-29	Cogn + EEG	0	145
	Kava extract	200mg tid PO	5 days	Volunteers	Healthy	12	co	24-37	Cogn + EEG	0	146
Miscellaneous											
ACE inhibitors	Captopril	50mg bid PO	6mo	Patients	AAMI	399	pg	>50	Cogn	0	149
Anti-anoxic agents	Sabeluzole	10mg bid PO	2mo	Patients	AAMI	53	pg	67	Clin + cogn	+	26
Metabolic enhancers	Actovegin	250ml (20%) PO	2wk	Patients	AAMI	18	co	50-80	Cogn + EEG	+	147
NSAIDs	Indomethacin	25mg tid PO	7 days	Volunteers	Healthy	20	co	59-73	Cogn	+	150
Phospholipids	Phosphatidylserine	100mg tid PO	12wk	Patients	AAMI	149	pg	50-75	Clin + cogn	+	148

a Specific age not reported.

Abbreviations and symbols: AACD = age-associated cognitive decline; AAMI = age-associated memory impairment; ACE = angiotensin converting enzyme; bid = twice daily; clin = clinical ratings; co = crossover; cogn = cognition; EEG = electroencephalogram; IN = intranasal; MAO = monoamine oxidase; NSAIDs = nonsteroidal anti-inflammatory drugs; pg = parallel groups; PO = oral; tid = 3 times daily; 0 = no effect; + = positive effect; ± = partial effect; ? = unknown.

onstrating the cholinergic activity of tacrine. This would have been interesting, since it has repeatedly been claimed that the progress in the search for cognition enhancers is hampered by the lack of an established control drug which is active in the treatment of AACD.

The relevance of studies into the cognition enhancing potential of nicotine may be further illuminated by the report of an inverse association between smoking and the incidence of AD among patients having a family history of dementia;[163] this suggests that nicotine may have a protective role in the aetiology of AD. Furthermore, acute nicotine administration has been shown to improve attention and speed of information processing in AD patients.[159,160] Whether these phenomena also apply to AACD remains to be seen, but the relationship between nicotine and cognition seems to be beyond dispute.

The acute blockade of nicotinic receptors induces cognitive dysfunction in healthy volunteers;[164] the degree of cognitive dysfunction induced by nicotinic blockade appears to be age-related.[165] Very recently, it was reported that nicotine enhances both glutamatergic and cholinergic synaptic transmission and that its mechanism of action is not postsynaptic agonism, but to enhance excitatory transmission by activating presynaptic nicotinic acetylcholine receptors.[166]

3.5 Monoaminergic Enhancers

Diminished catecholamine function is implicated in dementing illness of the elderly and may also be important in AACD. The positive mnemonic effects of adrenergic agonists in the treatment of memory impairments in aged nonhuman primates and in patients with Korsakoff's disease have motivated studies of these drugs in persons with AAMI, in which deficient central noradrenergic function is also implicated.[6] It has also been suggested that noradrenaline (norepinephrine) is crucial in certain cognitive functions associated with the frontal lobes, particularly the prevention of distractability by irrelevant stimuli.[167,168]

There is some evidence that serotonin exerts an inhibitory influence on learning and memory and also that changes in the serotonin system occur with aging.[169] Cognitive improvement during therapy with serotonin reuptake inhibitor antidepressants, particularly when administered to elderly patients who are cognitively impaired and depressed, are a topic of current interest that we chose not to address in this paper. Specific interest goes to serotonin 5-HT_3 antagonists, compounds that have, among other applications, specifically been targeted as cognition enhancers.[170]

Inhibitors of monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) have specifically been considered for their cognition enhancing properties in neurodegeneration.[171,172]

Daily doses of the α_2-agonist guanfacine 0.1, 0.2, 0.4mg or 0.5mg were administered during a 4-week period to groups of 40 and 160 elderly people who met AAMI criteria. The data suggested that guanfacine may have modest mood-improving effects but had no significant effects on learning and memory.[136]

Almitrine/raubasine (almitrine bismesilate 30mg plus raubasine 10mg) was administered twice daily during a 6-month period to 155 elderly patients reporting cognitive disorders and displaying an objective cognitive impairment. Evaluations included a visual analogical self-rating scale and psychometric tests. Statistical analysis did not show any significant difference between the almitrine/raubasine and placebo groups concerning changes in assessment criteria from baseline to treatment. However, *post hoc* division of the patient groups into qualitatively different subgroups according to baseline data, followed by statistical re-analysis, led to the erroneous suggestion that almitrine/raubasine enhanced concentrated attention in patients with mild to moderate impairment of this function.[137]

A clinical trial in which the serotonin 5-HT_3 antagonist ondansetron in doses of 0.01, 0.25 or 1.0mg was administered twice daily during a 12-week period to 198 elderly patients with AAMI showed significant improvements in some tests of memory performance after ondansetron 0.25m compared with placebo.[139]

Although theoretically there would have bee much to be expected from monoaminergic stimu lants, the clinical evidence is generally weak. Th assertion that the noradrenergic system appears t be involved in the focusing of attention,[167] woul bear relevance for AACD. Focused attention, a measured by the Stroop effect, was shown to be on of the most sensitive cognitive functions to declin with advancing age.[173] Unfortunately, none of th reviewed studies included such a test, but focuse on memory instead.

It is not very likely that dexamphetamine wil be applied in large scale trials, but the result whic showed that a low dose of the general catechol aminergic stimulant dexamphetamine could act a a cognitive enhancer, without adverse effects,[106 could have some impact as to new developments with this category of substances.

MAO type-B inhibitors have been considered as therapeutic agents for AD[174] and as nonspecific cognitive enhancers,[175] but application as stimulants appears to have failed.[102] The finding that a MAO type-A inhibitor, moclobemide, attenuated scopolamine-induced cognitive dysfunction[109] may indicate that this substance increases cholinergic neurotransmission and hence may have a multi-neurotransmitter effect, since its primary mode of action is increasing the circulating levels of noradrenaline and serotonin. Although there are many studies on the cognitive effects of these drugs in depressed patients, these agents have not yet been investigated primarily for their effects in AACD, but perhaps may be suited for use in patients with a combination of AACD and depression in old age.

The theory of indirect cholinergic facilitation by serotonin 5-HT_3 antagonists is very well described and seems to explain the positive results obtained in their application with the scopolamine model of cognitive dysfunction and also in AAMI.[108,139] Their additional anxiolytic potential perhaps calls for application to another subclass of AACD. A de-

finitive positive conclusion is difficult, however, after only one clinical trial.

3.6 GABA-ergic Agents

Benzodiazepines, the best known anxiolytics and hypnotics of the past 3 decades, act as agonists at the GABA-benzodiazepine receptor complex. Flumazenil is an antagonist and can hence completely and immediately stop the action of a benzodiazepine. Another class of drugs, the β-carbolines, also have affinity for the GABA-benzodiazepine receptor complex and act as inverse agonists, antagonists or partial inverse agonist/antagonists.

It has been hypothesised that if sleepiness is associated with increased levels of some kind of endogenous benzodiazepine ligand, the antagonism of flumazenil would immediately 'wake up' a sleeping or sleepy person and hence maintain vigilance.[176] An attempt to test the vigilance enhancing properties of flumazenil in sleep-deprived patients showed that this effect, if it existed at all, was very transient and was immediately followed by a vigilance decrement.[177] Nevertheless, flumazenil remains an interesting substance, particularly from a theoretical point of view relating to models of amnesia and because of its highly specific pharmacological action.[50]

β-Carbolines with antagonist or partial inverse agonist properties at the GABA-benzodiazepine receptor complex have been hypothesised to possess the property of disinhibiting cholinergic neurons of the basal forebrain.[57] This hypothesis was tested in humans, by means of the intravenous administration of the β-carboline ZK 93426 0.04 mg/kg or placebo, after pretreatment with scopolamine.[113] ZK 93426 did not improve the scopolamine-induced memory deficit and thus cholinergic stimulation by β-carbolines could not be demonstrated in humans.

3.7 Aminoacidergic Agents

Age-related changes in NMDA receptors have been found in cortical areas and in the hippocampus of many species. On the basis of a variety of experimental observations, it has been suggested that the decrease in NMDA receptor density might be one of the causative factors of the cognitive decline which occurs with aging. Based on these findings, several strategies have been developed to improve cognition by compensating for these NMDA receptor deficits.

The glutamate NMDA receptor can be modulated by glycine. Under appropriate conditions, stimulation by the amino acid glutamate results in long term potentiation (LTP) of future neural stimuli.[178] The most promising approaches are the indirect activation of glutamatergic neurotransmission by agonists of the glycine site or the restoration of the age-related deficit of receptor density by several nootropic drugs.[179]

Milacemide and cycloserine are 2 drugs which stimulate the strychnine-insensitive glycine binding site and hence might facilitate NMDA-mediated neural transmission. Milacemide was administered in doses of 1200mg on 2 consecutive days to 32 young and 32 elderly volunteers. Relative to placebo, milacemide facilitated the speed and quality of retrieval of learned words.[141] The efficacy of cycloserine 1, 5 and 15mg administered twice daily was investigated in 340 patients with AAMI using computerised assessments of memory and attention. The results only showed nonsignificant trends of improvement.[140]

It has been demonstrated that NMDA antagonists are active in humans, but one of these studies[117] provided the only negative result in this review: a putative cognition enhancer, milacemide, producing cognitive impairment. This could be explained by the potential neurotoxicity of this type of substance, but could also be explained by the hepatotoxicity of the drug. The problem of neurotoxicity could have been overcome with cycloserine,[114] a partial agonist/antagonist of NMDA. Furthermore, the clinical trial with cycloserine in AAMI showed some positive effects after 2 weeks of administration, but not at 12 weeks.[140] Perhaps tolerance to the intended positive effects of the drug nullified the treatment response.

3.8 Methylxanthines

As early as in 1901, the effects of caffeine on cognition were studied in humans. Improved comprehension and greater speed and accuracy in information processing, particularly evident under conditions of fatigue, were noted.[180] Improved performance on psychological tasks has, since then, frequently been reported after caffeine intake in healthy volunteers, even with doses as low as 32mg.[181]

The methylxanthines, caffeine and theophylline, are generally viewed as CNS stimulants, but recently their identification as adenosine$_{A1}$ receptor antagonists[182] has stimulated research into their effects on memory and cognition. A study investigating the effect of age on response to caffeine showed that the stimulant effects of caffeine predominated in young people, whereas the cognition enhancing effects of caffeine were seen in the elderly.[183] Adenosine antagonism is assumed to be the most important mechanism for explaining the effects of caffeine on behaviour.[184,185] Potential cognition enhancers include adenosine$_{A1}$ antagonists, since inhibitory adenosine$_{A1}$ receptors have been found on cholinergic terminals in the hippocampus and the cortex.[186]

Although many studies have investigated the acute effects of caffeine in single-dose paradigms, controlled studies on the subchronic and chronic use of caffeine are difficult to find. There is however, one very interesting study describing a positive effect of caffeine on cognitive function, including memory.[187] The study involved 7414 people distributed over age groups of about 20, 30, 40, 50 and 60 years. A positive linear relationship existed between daily coffee consumption and cognitive performance. Older people appeared to be more susceptible to the performance-improving effects of caffeine than younger people.[187]

Although caffeine is widely known as a CNS stimulant, it also seems to be a cognition enhancer. An explanation might be that its adenosine antagonism has a supplementary effect on cholinergic function. That is, it doesn't affect memory in people when they are young and cholinergic function is optimal. When cholinergic dysfunction is induced experimentally or naturally, due to aging, caffeine might exert a positive effect on memory through this system.

It is difficult to imagine a controlled clinical trial with caffeine, but it would be feasible to study the relationship between age, daily caffeine intake and changes thereof, and cognitive function, between and within volunteers. Furthermore, in clinical trials with putative cognition enhancing drugs, one should keep track of the amount and time of daily caffeine consumption. The results could then either be magnified or attenuated after correction for caffeine intake.

3.9 Vitamins

Although traditionally it has been assumed that the vast majority of those living in industrialised countries have an adequate micronutrient intake, there is growing interest in the suggestion that an increased vitamin intake may have advantages for at least some people.[142]

It has been argued that the first symptoms associated with micronutrient deficiency are psychological.[188] An association was demonstrated between cyanocobalamin (vitamin B_{12}) blood level and cognitive performance independent of age.[189] Furthermore, short term supplementation with nicotinamide (vitamin B_3) was shown to improve memory.[190] On the other hand, a review of 53 controlled trials in humans[191] on the effects of nicotinic acid (niacin), pyridoxine (vitamin B_6) and multivitamins on mental functions established that virtually all trials showed serious methodological shortcomings. The only positive results were found with very high dosages of pyridoxine combined with magnesium in autistic children.

Positive effects of pyridoxine supplementation (20 mg/day for 3 months) in 38 healthy elderly men compared with 38 controls who received placebo and were matched for age, plasma pyridoxal-5-phosphate concentration and intelligence score, yielded a modest, but significant, improvement of storage of information in long term memory, but not with respect to the phasic pupil response, an

index of mental effort. It was suggested that cognitive effects are primarily associated with a certain range of pyridoxine status increment.[143]

Ten times the recommended daily dose of 10 vitamins [retinol (vitamin A) 3334IU, thiamine 14mg, riboflavin 16mg, pyridoxine 22g, cyanocobalamin 0.030mg, ascorbic acid 600mg, tocopherol 100mg, folic acid 4mg, biotin 2mg, nicotinamide 180mg] or placebo was administered to 27 healthy volunteers for 1 year. At the end of the treatment period, there was some evidence of improved attention in women only and, also in women, an association between improved thiamine status and improved cognitive performance.[142]

Pyritinol is a synthetic compound containing 2 molecules of pyridoxine joined by a disulphide bridge. Despite this similarity with pyridoxine, pyritinol has no vitamin action but is regarded as an encephalotropic or nootropic compound. Twelve healthy volunteers received pyritinol 600 or 1200 mg/day for 3 days. Significant improvements in critical flicker fusion and choice reaction time, but not of memory, were found.[144]

The possibility of vitamins as cognition enhancers remains obscure, despite some remarkably well conducted experiments and trials. The case for pyridoxine does not seem to be very strong.

The association of thiamine deficiency with memory dysfunction and cognitive disorders has been related to an impairment of cholinergic activity,[192] and this association was shown in humans using the scopolamine model. Thiamine has been advocated for the treatment of cognitive dysfunction and fatigue of central origin (asthenia), prevalent after prolonged physical exercise in endurance athletes[193] but also in aging.[194] It has been suggested that the cognition enhancing potential of thiamine in AD is equivalent to that of physostigmine and, because of its general lack of adverse effects, would deserve the benefit of the doubt.[125] Whether this is also the case in AACD remains to be demonstrated.

3.10 Herbal Compounds

Currently, herbal compounds known by ancient medicine in the Far East are experiencing growing popularity as cognition enhancers. One such compound is ginkgo biloba extract. The main indication of interest is that of 'cerebral insufficiency', a condition related to cognitive decline of organic origin. Among the proposed mechanisms of action are the antioxidant effects of flavonoids, ingredients of ginkgo biloba extract.

A review of 40 clinical trials investigating the effect of ginkgo biloba extract has been published.[195] Only 8 clinical trials were judged to be of good quality[196] and these revealed mainly positive effects of ginkgo biloba extract, although most trials did not include cognitive assessments. A comparison was made between the best clinical trials of ginkgo biloba extract and ergoloid mesylates (codergocrine mesylate), and it was concluded that the compounds were of equal efficacy.[195]

More recently, only 1 study has been conducted in which the brain bioavailability of 3 days of treatment with ginkgo biloba extract 40, 80 and 160mg 3 times daily was investigated in 24 healthy volunteers.[145] No effects were found on cognitive performance but significant changes in EEG patterns were detected, without changes of indices of alertness, indicating the bioavailability of ginkgo biloba.

Another herbal compound, kava root extract, was assessed for its effects on recognition memory using an ERP paradigm in 12 healthy volunteers who were administered 200mg 3 times daily over a 5-day period.[146] Although trends towards improvement were reported, no significant effects of kava root extract were seen.

3.11 Other Compounds

3.11.1 Anti-Inflammatory Agents

Although classically defined inflammation is not a characteristic of the pathologically aging brain, numerous acute phase reactants and immune-related markers have been found. Furthermore, retrospective studies suggest that rheumatoid arthritis patients, many of whom could be expected to be taking anti-inflammatory medication, have a lower incidence of AD than the general population. This has led to the hypothesis that anti-

inflammatory agents might be effective as cognition enhancers.

Anti-inflammatory drugs may have neurotoxic properties, suggesting that they cross the blood-brain barrier. The nonsteroidal anti-inflammatory drug (NSAID) indomethacin has been shown in a very small controlled clinical trial to exert some protective effects on cognitive decline in patients with mild to moderate AD.[197]

Indomethacin 25mg was administered 3 times daily to 20 healthy elderly volunteers during an 8-day period. Arousal, attention, integration, coordination, memory and mood were investigated using a battery of psychomotor tests and clinical ratings. Assessments were performed before and after the first and last doses. While critical flicker fusion threshold significantly decreased after the first dose, a beneficial effect on choice reaction time latency was seen both after acute and continuing administration of indomethacin. No change was seen in performance on the symbol-digit substitution test, the continuous attention task and in anxiety and depression scores. Cognition may improve in healthy volunteers following indomethacin administration, whereas attention and psychomotor speed remained unaffected.[150]

3.11.2 Anti-Anoxic Agents

Anti-anoxic agents protect against hypoxia and ischaemia by improving brain metabolism. Sabeluzole 10mg or placebo was administered twice a day during a 2-month period to 53 elderly patients complaining spontaneously about their memory. They were selected if they fulfilled the AAMI-criteria and if they were poor performers on a Selective Reminding Procedure (SRP). No significant sabeluzole-placebo difference was found. However, significant improvements in learning, memory (but not on the SRP) and verbal fluency were found within the sabeluzole treatment group.[26] This within-group effect could be an indication of a genuine treatment effect that did not emerge in the between-group analysis because of the small sample size and short treatment period.

3.11.3 Phospholipids

Phosphatidylserine 100mg administered 3 time daily during a 12-week period to 149 AAMI pa tients led to significant improvements relative t placebo on performance tests related to learnin and memory tasks of daily life. The investigator reported that analysis of clinical subgroups sug gested that persons within the sample who per formed at a relatively low level prior to treatmen were most likely to respond to phosphatidylserine Within this subgroup, there was improvement o both computerised and standard neuropsychologi cal performance tests, and also on clinical globa ratings of improvement.[148]

Again this is an example of *post hoc* split-hal evaluation on the basis of observed data, an unac ceptable way of analysing and interpreting data rendering the conclusion drawn by the authors, i terms of the treatment being a promising one fo this indication, less likely.

3.11.4 Metabolic Enhancers

Actovegin is a protein-free metabolically activ haemoderivative which improves oxygen and glu cose utilisation. The psychotropic effects of 250m actovegin 20% were investigated in 18 patient with AAMI during a period of 2 weeks. Pharmaco dynamic evaluations were carried out after the ad ministration of a single intravenous infusion on da 1, and before and after an additional superimpose infusion on day 15.

EEG brain mapping demonstrated that acto vegin improved vigilance accompanied by im proved cognitive performance, increased physio logical arousal and increased P300 amplitude. This confirmed the hypothesis that nootropic drugs may influence the P300 amplitude by improving the availability of cognitive processing resources.[198] Time-efficacy calculations exhibited more effect after subacute than acute administration, with the pharmacodynamic maximum after the superimposed dose.[147]

3.11.5 ACE Inhibitors

ACE inhibitors have been shown to protect, enhance or restore performance in various learning and memory paradigms in animals.[149,199] These

drugs may produce their cognitive effects through an indirect action on the cholinergic system. A possible mechanism for the action of ACE inhibitors on the cholinergic system is provided by the finding that angiotensin-II (the formation of which is prevented by ACE inhibitors) can inhibit acetylcholine release in *in vitro* preparations of rodent and human cerebral cortex.[130]

Analysis of clinical trials over a treatment period of 6 months with captopril 50mg administered twice daily to 280 normotensive patients with AAMI revealed little or no evidence that captopril improved cognitive performance.[149] In a recent review on the effects of ACE inhibitors on cognitive function, it was concluded that these agents do not have a deleterious effect on cognitive function.[199] No evidence for cognitive improvement by ACE inhibitors in humans was found.

3.11.6 Glucose

The actions of glucose in the brain may be related to the role of the compound as a precursor for the formation of acetylcholine and many other neurotransmitters. The importance of glucose further supports the hypothesis that many cognition enhancing substances produce their effect by means of increased glucose utilisation.[200]

The nootropics, amphetamine and vasopressin stimulate the adrenals resulting in peripheral catecholamine release. Subsequently, the liver is induced to release glucose into the blood. Glucose passes through the blood-brain barrier and increases the availability and uptake of glucose in the brain. This is suggested by the observation that some substances, such as piracetam, aniracetam, pramiracetam, oxiracetam, vasopressin and amphetamine, particularly those that do not cross the blood-brain barrier, are ineffective after adrenalectomy.[200] Furthermore, cognitive function, i.e. learning and memory, is correlated with glucose regulation in aged animals and humans.[200,201]

3.11.7 Compounds with a Dual Mode of Action

S 120242 is a compound whose mechanism of action involves facilitation of noradrenergic and vasopressinergic systems.[202] Repeated administration of doses of S 120242 in the range of 10 to 200mg twice daily were claimed to be capable of correcting AACD in otherwise healthy elderly volunteers in a dose-dependent fashion.[138]

4. Discussion

4.1 The Patient Population as a Target for Drug Studies

With respect to the nature of AACD, several remarks can be made. The AAMI concept was well formalised, allowing for the possibility to perform many clinical trials on the same target population. This target population, however, was almost as big as the aging population itself and for that reason, was very heterogenous. One particular aspect of AAMI was the presence of memory complaints. The presence of memory complaints was operationalised as a score on a questionnaire and the 'patient' did not need to have complained about him- or herself. So, in some cases, this population was described as: 'elderly people fulfilling the AAMI criteria'. The core of the problem is, in our opinion, not so much that cognitive aging, or AACD, is not a disease according to a classic medical model, but the fact that the inevitable consequences of a 'natural phenomenon' (aging) is in many cases indistinguishable from the consequences of present or past disease states.

Many age effects reported in the literature can be largely explained by suboptimal brain functioning induced by factors other than aging *per se*. These age-extrinsic factors have been called biological life events (BLE).[203] Examples of BLE are repeated exposure during one's lifetime to: general anaesthesia, organic solvents, neurotrauma and chronic use of psychotropic medications or alcohol. It may be important to discern various subgroups within the heterogeneous group of individuals without dementia but with complaints of impaired cognitive functioning, e.g. those with BLE and those without.[4]

Patient groups for drug studies can be made more homogeneous, which would improve the detection of possible drug effects. The rationale is that the pathogenesis of the cognitive decline can

be expected to differ for the various subgroups of elderly people with complaints. Examples of this approach are studies investigating the effects of cognition enhancers in patients suffering from the cognitive impairment due to neurotrauma,[33,204] alcoholic organic brain syndrome,[205] epilepsy,[206] organic solvent exposure[207] and hysterectomy.[208]

4.2 Methods Used for Treatment Evaluation

The use of test batteries covering an array of cognitive functions is seldom explained and therefore one may wonder why so many tests were carried out to assess the answer to one simple question – does this drug enhance cognition? The field suffers from a lack of explicit standardisation, although it has often been specified that this is what is required for the contents of a cognitive test battery applied for drug testing.[209,210]

The best approach is, in our opinion, always to use at least 2 assessments of the same cognitive function under conditions of varying task load, or difficulty. In the case of cognition enhancing drugs, the relevant components of a test battery should at least include objective assessments of memory storage and retrieval (immediate and delayed recall, and recognition of learned material), speed of search in short term memory (e.g. according to the Sternberg paradigm), focused attention, divided attention, vigilance and estimates of information processing and psychomotor speed (choice reaction time).

Regarding this problem, research in AD is more advanced because an international standardisation of effect measures (e.g. Alzheimer's Disease Assessment Scale, CIBIC) has been accomplished, although the specificity and the sensitivity of these measures may be questioned. In the domain of AACD, there is no such standardisation. Some good examples exist of cognitive test batteries used in several of the AAMI clinical trials.[211,212] One such test battery was entirely based on the assessment of memory functions,[211] without controlling for levels of alertness or vigilance. The other cognitive test battery,[212] which has been used in a number of clinical trials and experiments, yields many measures of cognitive speed, while no free recall measures of memory functions are taken.

The best solution would perhaps be to apply tests that assess both memory performance and measures of cognitive speed that have been shown to be sensitive to aging and drug effects, and are applicable within standard clinical neuropsychological assessment.[33,213]

Another problem often encountered in using test batteries providing many dependent measures is that of an increased type I error. An often heard criticism is therefore that using a battery of cognitive tests always leads to some kind of a positive result. However, it should be noted that it is a matter of good scientific practice to specify an hypothesis explicitly *a priori* and fully operationalise these into descriptions of outcome parameters. This allows for distinctions to be made between primary and secondary outcome parameters.

In clinical trials, the former refer to the 'intent-to-treat' analysis. If these basic scientific rules are adhered to, there is nothing against using a test battery yielding a wide range of dependent measures. In fact, it often yields more information than global measures.[209] Furthermore, it is of interest in the search for cognition enhancers whether hypotheses about the effects of a substance are in any manner specific as to the cognitive functions that are the target of enhancement.

Some distinctions have been made, particularly regarding the specificity of memory enhancement, but if a drug simply claims to enhance cognition, indeed, this is an implicit hypothesis stating that the performance on all tests should be significantly enhanced by the particular treatment. In such a case, compiling all the dependent measures into one very nonspecific, but sometimes sensitive performance index, may be a way to circumvent extensive statistical procedures.

In recent years, some drugs (the aminoacidergic agents) have been developed claiming to enhance long term potentiation (LTP) of memory consolidation. Such an hypothesis lends itself for relatively precise operationalisation. It would not be necessary to observe enhanced performance on all

but a few dependent measures of cognition measuring precisely the expression of LTP, such as improved recall and recognition of learned material. In fact, the absence of effects on aspects of cognition that are not predicted is a primer in such a case. Whether eventual significant improvements are clinically relevant, remains a topic that can simultaneously be dealt with employing clinical rating scales.

With respect to the application of EEG measures, we feel that the application of this technique to demonstrate the brain bioavailability of a substance does not make much sense in relation to a demonstration of its efficacy. This does seem to be the case however, for the application of ERP paradigms such as P300. The latter provides a well defined measure of cognitive processing and as such seems to be a relevant index. If background EEG is changed, i.e. a change in the dominant rhythms in the EEG, this would initially indicate changes in parameters such as arousal, activation and vigilance.

4.3 Future Possibilities

One problem that this review has shown is that the many promising results from human models are rarely followed by successful results in large scale clinical trials. In some cases, the models are therefore blamed because of their lack of predictive validity. However, if after demonstrating the cholinergic activity of a substance, it appears that no good clinical results are obtained with it, then perhaps one ought to conclude that the clinical population did not have a cholinergic deficit. In other words, validity of the scopolamine model for assessing the cholinergic activity of a drug seems beyond doubt, but whether it adequately mimics AACD is a matter of great dispute.[214]

Rather than to do away with these kind of models, it might be a better strategy to devise new human models and refine current ones. In the future, the scopolamine model will probably be replaced by more selective and specific models employing muscarinic m_1-antagonists, such as biperiden,[215] and nicotinic antagonists like mecamylamine,[164,165] to model aspects of AACD and to test new drugs specifically aimed at improving those aspects of cholinergic transmission. For example, the new selective and specific muscarinic m_1-agonists that are currently under investigation for AD, should reverse the cognitive deficits in humans induced by scopolamine or biperiden, but not those induced by mecamylamine. If these drugs would not satisfy such hypotheses, they would not be true m_1-agonists and hence could as such be discarded. It is also evident that the ultimate demonstration of clinical efficacy of substances in patients are perhaps more important until truly predictive human models are established. The value of human models is that they are of help to find out if drugs really do what they claim to do in humans.

Regarding the benzodiazepine model of amnesia, the possible refinement of this model has already been mentioned. When patients were pretreated with the specific benzodiazepine receptor antagonist, flumazenil, the sedative and attentional effects of diazepam were blocked, but a marked impairment in episodic memory still occurred. This selective pattern of cognitive dysfunction may serve as a model for clinical cognitive syndromes.[112,216,217]

A variation of the hypoxia model is that of hyperventilation-induced cognitive dysfunction. This model has previously been shown to be more valid for the simulation of ischaemic events in the brain than the hypoxia model and also that it is a sensitive model to test the neuroprotective effects of nootropic drugs such as aniracetam.[60] Recently, hyperventilation-induced cognitive dysfunction was demonstrated employing a variety of cognitive tests.[218]

In principle, models of cognitive dysfunction are pharmacological, physiological or psychological conditions, known to cause cognitive dysfunction. In this review we have seen several relatively little used applications such as acute alcohol intoxication and sleep deprivation.[64] Many more of those models exist (for example, all those in which the availability of resources for cognitive processing are manipulated) and could be tried for the

screening of cognition enhancers. Whether or not such models have direct relevance for the aetiology of AACD is not the most important question. As long as it is not entirely clear what a drug does in terms of biological and pharmacological modes of action, behavioural models in humans may supply the evidence to the claimed effect of cognition enhancement.

5. Concluding Remarks

In general, it can be concluded that there are many active substances that have been shown to be capable of enhancing cognition in individuals without dementia. The question as to the reliable demonstration of clinical efficacy of cognition enhancers in AACD however, is still difficult to answer. We deliberately chose to include as many reports of clinical trials as possible, thereby accepting the impossibility to critically comment on some of the findings. The compounds that have been under investigation for many years, such as nootropics, ergot alkaloids, neuropeptides, precursors of acetylcholine, monoaminergic enhancers, GABAergic agents, ACE inhibitors and calcium antagonists, do not seem to be of use in AACD.

Recent developments in research with cognition enhancers for the treatment of AD, i.e. cholinesterase inhibitors, muscarinic agonists and multitransmitter substances, also promise new developments in AACD. The data on these substances in individuals without dementia are interesting, but are currently insufficient to predict the benefits and costs of their use in the treatment of AACD. The substances that have been the most promising, as predicted from theory, animal research and human experimental studies, were the compounds aimed at facilitating glutamate or NMDA-mediated neurotransmission and the compounds aimed at indirectly facilitating cholinergic transmission via the antagonism of serotonin 5-HT_3 receptors. These have been demonstrated to be active in experimental human studies, followed by disappointing results in the clinic.

If a substance can be demonstrated to exert positive effects on cognition in elderly people in a reliable manner, and if that substance would lack adverse events, it would be of enormous value, regardless of the question whether we know what it does in the human brain or how it works. In Germany and France, piracetam, ergoloid mesylates and ginkgo biloba extract are among the most commonly prescribed drugs. This illustrates that economical, political and sociological factors as well as fear of dementia and expectancy, rather than proof of efficacy, determine prescription.[219] Caffeine, nicotine and vitamins are examples of substances that are consumed on a large scale, presumably with the primary aim of improving and sustaining concentrations in the body, but the evidence that they might also improve memory and cognition is increasing. There are many more substances which have cognition enhancing properties, but to a limited extent, rendering them inefficacious for AACD. The substance that fulfils all prerequisites does not (yet) exist. In the meantime, perhaps this situation will allow researchers and clinicians to agree on the target symptoms and population characteristics of AACD, as well as on standardisation of models and measures of cognition necessary to demonstrate the effects of cognition enhancing drugs.

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